Thrombotic risk assessment in 185 WHO-defined essential thrombocythemia patients: single center experience

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Thrombosis risk in essential thrombocythemia (ET) patients can be assessed using different prognostic systems. Conventional risk factors include age more than 60 years and history of previous thrombosis. In addition, other factors such as JAK2 V617F mutations, cardiovascular risk factors, leukocytosis more than 11 × 10^9/l, thrombophilic factors and platelet count more than 1500 × 10^9/l are used in different hematology centers as high-risk features for thrombosis. Our study compared different risk model groups for thrombosis in 185 WHO-defined ET patients at the Hospital of Lithuanian University of Health Sciences Kaunas Klinikos. We found that patient distribution in low, intermediate- and high-risk groups varies using different risk stratification models. The biggest difference in risk assignment is evident in patients who are older than 60 years and have no other risk factors and in patients who are younger than 60 years but have other risk factors.
This observation suggests that new prospective randomized clinical trials are needed to better stratify patients at risk for thrombosis.

Key words: chronic myeloproliferative neoplasms, essential thrombocythemia, platelets, thrombosis.

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Introduction

Essential thrombocythemia (ET) is one of the bcr-abl negative myeloproliferative neoplasms. Diagnosis is made when 1) platelet count is higher than 450 × 10^9/; 2) patients have the *JAK2 V617F* mutation or another clonal mutation such as in the gene encoding the thrombopoietin receptor (*MPL*); 3) bone marrow reveals megakaryocyte proliferation with large and mature megakaryocytes in the bone marrow [1]. Recent discovery of the calreticulin (*CARL*) gene is likely going to modify the diagnostic criteria of ET [2] as there are ET patients who have the *CARL* mutation but do not bare *JAK2 V617F* and *MPL* mutations.

The most common complications associated with ET are thrombosis, bleeding and myelofibrosis. Thrombosis can be life-threatening, so it is important to identify patients at risk for thrombotic complications. Thrombosis risk assessment is still a matter of debate as different research groups use different risk criteria. To date, the most widely used are the conventional evidence-based criteria. Based on them, high-risk factors for thrombosis are age > 60 years and a history of previous thrombosis [3]. The intermediate-risk group encompasses patients whose age is between 40–60 years, whereas patients under 40 years fall into the low-risk stratum [4]. However, the British Committee for Standards in Haematology (BCSH) uses a platelet count of > 1500 × 10^9/l as an additional high-risk factor (Table 1). For comparison, the Czech Collaborative Group for Ph negative Myeloproliferative diseases (CZEMP) identifies high-risk patients by additional factors such as platelet count > 1000 × 10^9/l, thrombophilic status and microcirculatory symptoms [5].

In 2012 the International Working Group of Myelofibrosis Research and Treatment (IWG-MRT) developed the International Prognosis Score for ET (IPSET) to help predict survival for ET patients at diagnosis. The same model was able to predict thrombosis [6] (Table 2). Additionally, the International Prognosis Score for Thrombosis (IPSET-T) risk stratification was proposed by Barbui and colleagues [7]. It includes not only the patient's age and history of thrombosis as risk factors but also *JAK2V617F* mutation and cardiovascular risk factors (Table 3). In contrast to *JAK2V617F* mutation, *CARL* positive patients showed decreased thrombosis risk, and incorporating it in the IPSET-T model does not modify the thrombosis risk [8].

The purpose of this study was to compare the outcomes of patients with ET based on different risk stratification systems. We evaluated 185 WHO-defined ET patients at the Hospital of Lithuanian University of Health Sciences Kaunas Klinikos.

Material and methods

This was a retrospective, cohort study at a single university hospital. Our survey included 185 patients who were diagnosed with ET according to 2008 WHO essential thrombocythemia diagnostic criteria. Patients diagnosed with ET before 2008 according to Polycythemia Vera Study Group (PVSG) criteria were revaluated for WHO diagnostic criteria. Data were collected from medical records and interviews obtained during patients' visits to a hematologist. All patients were asked to complete a cardiovascular events and risk factors questionnaire. On repeated visits during follow-up, the history of thrombosis was taken. Cardiovascular risk factors were arterial hypertension, overweight, smoking, diabetes mellitus, and hypercholesterolemia. Thrombotic events were defined as major: acute myocardial infarction, unstable angina pectoris, ischemic stroke and venous thrombosis. All patients were evaluated for risk factors using four different systems (Table 4, Fig. 1). The study was approved by the regional ethics committee.

Results

The mean age of our study cohort was 62 years (range 17–90); they were predominantly female patients (67.2%). The mean platelet count was 765 × 10^9/l (range 450–2268 × 10^9/l), mean hemoglobin concentration 132 g/l (range 120–178 g/l), and mean leukocyte count 9.9 × 10^9/l (range 4–22 × 10^9/l). The mean disease duration was 47.31 months (range 1–142). Splenomegaly was analyzed by physical examination. Palpable splenomegaly was present in 16 (8.6%) patients. There was thrombosis history in 47 (25.4%) patients, thrombosis before diagnosis in 35 (18.9%) patients, and after diagnosis in 12 (6.5%) patients. Most events were arterial (41, 87.2%), 5 (10.6%) were venous, and 1 (2.1%) patient had both arterial and venous events.

One or more cardiovascular risk factors were identified in 66 (35.7%) patients, 2 of them have 3 risk factors (arterial hypertension, diabetes mellitus and overweight), 35 patients have 1 risk factor, and the other 66 patients have 2 risk factors. 152 (82.2%) were positive for *JAK2V617F* mutation.

According to conventional thrombosis criteria we identified 126 high- and 59 low-risk patients in our cohort. From the high-risk group 23 patients had thrombosis history and were older than 60 years at diagnosis, 91 patients were older than 60 at diagnosis with no thrombosis, and 13 patients were younger than 60 with thrombosis.

According to the prognostic model IPSET, we identified 56 patients as high-risk, 87 patients as intermediate-risk and 42 patients as low-risk group.

Table 1. BCSH risk stratification [4]

High risk	Intermediate risk	Low risk
Age > 60 years	Age 40–60 years	Age < 40 years
Prior thrombosis		
Platelet > 1500 × 10^9/l		

Table 2. IPSET risk stratification [6]

Risk factors	Scores		
	0	1	2
Age	< 60		≥ 60
WBC × 109/l	< 11	≥ 11	
History of thrombosis	No	Yes	

**Low risk, score 0; intermediate risk, score 1–2; high risk, score 3–4*

Table 3. IPSET-Thrombosis risk stratification [7]

Risk factor	Score*
Age > 60	1
Cardiovascular risk factors	1
Previous thrombosis	2
JAK2 V617F	2

**Low risk, score 0–1; intermediate risk, score 2; high risk, score ≥ 3*

According to the IPSET-Thrombosis model, 118 patients were high-risk, 44 were intermediate-, and 23 low-risk.

According to the BCSH risk stratification 127 patients were high-risk, 28 intermediate-, and 20 low-risk.

Discussion

The most common cause of ET morbidity and mortality is thrombotic complications. Therefore it is important to establish thrombosis risk factors at the time of diagnosis in order to decide proper treatment options. The purpose of our survey was to evaluate the clinical usefulness and relevance of four thrombosis scoring systems (conventional, IPSET, IPSET-T, BCSH) in our cohort of 185 2008 WHO-defined ET patients.

The conventional risk factors are age and previous thrombosis. Patients under 60 years old without previous thrombosis are low-risk. In our cohort 59 (31.9%) patients from 185 are low-risk using these aforementioned risk factors not requiring cytoreductive treatment. According to IPSET-T only 8 (13.6%) patients without any other factors (score 0) from those 59 and 4 (6.8%) patients with cardiovascular risk factors only (score 1) belong to the low-risk group. So, only 20.3% of 185 patients younger than 60 remain in the low-risk group when applying the new

Table 4. Classification of 185 ET patients according to different risk scoring

Risk group	Conventional	IPSET	IPSET-T	BCSH
High	126	56	118	127
Intermediate	–	87	44	38
Low	59	42	23	20

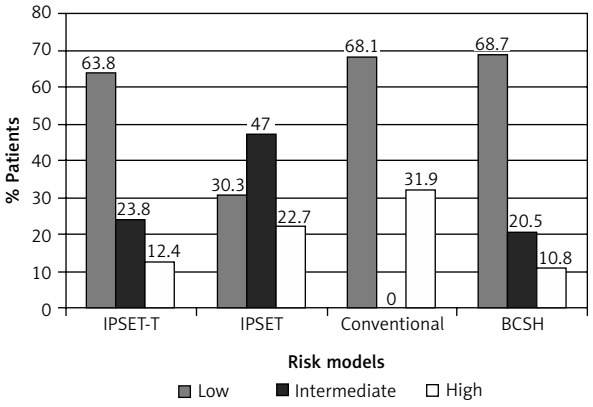

Fig. 1. 185 patients risk groups

IPSET-T criteria. The majority of these 59 low-risk patients from our cohort transfer to the intermediate-risk group: 36 patients (61.0%) with *JAK2V617F* positive only (score 2). Ten patients (16.9%) from 59 patients are younger than 60, *JAK2V617F* positive with one of the cardiovascular risk factors (score 3). They would be categorized as high-risk according to IPSET-T. In this case these aforementioned 16.9% of patients probably would require cytoreductive treatment already, despite being under 60 years old and having no previous thrombosis, if we use the IPSET-T model at diagnosis. Nevertheless, our data show that almost 80% of low-risk patients under 60 years old are reclassified to the IPSET-T intermediate- and high-risk group category. This group of patients would benefit from a prospective, randomized clinical trial in order to define optimal treatment modality. When using BCSH criteria this low-risk group decreases even more, because only 20 (10.8%) patients are younger than 40 years with no other risk factors.

Patients older than 60 either have thrombosis history belong to the high-risk group using conventional risk factors. This group of patients would benefit from cytoreductive therapy. There are 126 (68.1%) high-risk patients according to conventional risk factors in our cohort. This group consists of 91 (72.2%) patients older than 60 with no thrombotic events, 23 (18.3%) older than 60 with thrombosis history, and the remaining 12 (9.5%) patients are younger than 60 with previous thrombosis. 11 (12.1%) patients from all who are older than 60 without *JAK2V617F* mutation, with no cardiovascular risk factors and with no previous thrombosis would belong to the low-risk category according to IPSET-T (score 1). Actually this group could be even higher, but our cohort is 82% *JAK2V617F* positive. It is contrary to the risk model with conventional risk factors, because these 11 patients would belong to the high-risk group. It means that these 12.1% of patients from the conventional high-risk group would transfer to low-risk IPSET-T, probably requiring observation only or possibly antiplatelet therapy. Otherwise, they may be over-treated with cytoreductive treatment.

Age in the IPSET classification has the highest impact on thrombosis risk level. Only patients older than 60 with leukocytosis more than 11×10^9/l and previous thrombosis belong to the high-risk group according to IPSET. From our patients, 56 (30.3%) fell into the high-risk category based on the IPSET classification. Interestingly, this number of patients is the smallest when comparing all other risk models (BSCH, IPSET-T, conventional).

Only one third of 185 patients (44; 23.8%) according to IPSET-T belong to the intermediate-risk group. One (2.3%) patient is under 60 years old with previous thrombosis, *JAK2V617F* negative and with no cardiovascular risk factors (score 2). Seven (15.9%) from these 44 patients are older than 60 with one or more cardiovascular risk factors (score 2). 36 patients (81.8 %) are *JAK2V617F* positive only (score 2). Almost half of all patients (47.6%) are categorized as intermediate-risk according to IPSET. 30 (34%) of these 88 patients are younger than 60: 10 (11.4%) patients (score 1) had previous thrombosis, 17 (38.6%) patients (score 1) had leukocytosis more than 11×10^9/l, and 3 patients (6.8%) (score 3) had both risk factors. It seems that adding leukocytosis more than 11×10^9/l as an independent risk factor for thrombosis scoring doubles the intermediate-risk group in the IPSET model. The high-risk group in IPSET seems to be the smallest when compared with other risk models.

To date, 12 patients from our cohort have had thrombosis after diagnosis. Adopting the IPSET-T model, 1 patient was in the low-risk, 1 in the intermediate-risk and 10 patients in the high-risk group. Due to small numbers of thrombotic events we were unable to perform a statistical analysis.

Management of ET patients largely depends on the patient risk group. Low-risk patients benefit from antiplatelet therapy. There is no prospective randomized clinical trial for aspirin use, although a retrospective study favors aspirin use compared to observation only [9]. Moreover, some experts recommend aspirin use even twice daily to prevent thrombosis [10]. If patients have extreme thrombocytosis with platelet count > 1000×10^9/l causing acquired von Willebrand syndrome or increased risk of bleeding, antiplatelet agents should be avoided [11]. There is no consensus in management approaches for patients in the intermediate-risk group. The group of experts of the Italian Society of Hematology (SIE) and the affiliate societies SIES (Italian Society of Experimental Hematology) and GITMO (Italian Group for Bone Marrow Transplantation) agree that at present there is no evidence to treat with cytoreductive medications these intermediate-risk patients and for further improvement of evidence-based data controlled randomized trials are needed [12].

Management of the high-risk group is well defined. Hydroxycarbamide (HU) together with low dose aspirin or anagrelide monotherapy is becoming a standard of care [11, 13, 14]. In patients aged under 40, interferon αis recommended [4]. Use of busulfan or pipobroman is usually restricted to ET patients older than 75 and only as second or third line therapy [13].

In conclusion: our results show that different risk assessment models stratify patients to different risk groups. There is a subset of patients that varies from the low- (20.7%) to high-/intermediate-risk group and from the high- (12.1%) to low-/intermediate-risk group according to different scoring systems that we use at diagnosis. In

our opinion, IPSET-T would be more rational to use, whereas it is based on four thrombosis criteria including *JAK2 V617F* mutation and determined the largest group of patients that need treatment compared with other models. New prospective randomized clinical trials are crucial, especially for ET patients older than 60 who have no other risk factors and ET patients younger than 60 years with no previous thrombosis but with other risk factors, in order to avoid over-treatment as well as insufficient treatment.

The authors declare no conflict of interest.

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